PATENT COOPERATION TREATY

REC'D 18 APR 2006
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 588.F	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/043969	International filing date *(day/month/year)* 29.12.2004	Priority date *(day/month/year)* 30.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07F9/44		
Applicant GILEAD SCIENCES, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 13 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.10.2005	18.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Fritz, M Telephone No. +31 70 340-3024

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043969

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-3, 5-26, 28-138	as originally filed
4, 27	received on 27.10.2005 with letter of 27.10.2005

Claims, Numbers

1-59	received on 27.10.2005 with letter of 27.10.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	33-36,39-50,52-59
	No:	Claims	1-32,37-38,51
Inventive step (IS)	Yes:	Claims	33-36,39-50,57-59
	No:	Claims	1-32,37-38,51-56
Industrial applicability (IA)	Yes:	Claims	1-59
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: SNOECK ET AL.: "Antivaccinia Activities of Acyclic Nucleoside Phosphonate Derivatives in Epithelial Cells and Organotypic Cultures" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 46, no. 11, November 2002 (2002-11), pages 3356-3361, XP002327372

D2: KEITH ET AL.: "Evaluation of Nucleoside Phosphonates and Their Analogs and Prodrugs for Inhibition of Orthopoxvirus Replication" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 47, no. 7, July 2003 (2003-07), pages 2193-2198, XP002327373

D3: CHRISTENSEN ET AL.: "In vivo anti-papilomavirus activity of nucleoside analogues includinh cidofovir on CRPV-induced rabbit papillomas" ANTIVIRAL RESEARCH, vol. 48, 2000, pages 131-142, XP002327374

D4: US 2003/072814 A1 (MAIBACH HOWARD I ET AL) 17 April 2003 (2003-04-17)

Amendments:

The proviso used in claim 1 that
"at least one Y^1 is -N(R^x)"
is a preferred embodiment which was present only for the compounds of formula IA according to claim 6 as originally filed (cf. claims 7, 46), however the definition of W^5 in the compounds I according to claim 1 covers subject-matter going beyond the scope of the compounds of formula IA and thus preferred embodiments having no basis in the application as originally filed.
The requirements of Articles 19(2) and 34(2)(b) PCT would be fulfilled for claim 1, if the definition of W^5 were restricted to representing a cyclopropyl group only.

In that case claim 1 would also cover only subject-matter which was actually searched.

Assuming that this modification was carried out claims 2-7 would also be allowable.

Claims 8-34 are, however, directed to preferred embodiments which are not comprised in the application as originally filed and thus do not fulfil the requirements of Articles 19(2) and 34(2)(b) PCT.

Claims 35-38 are allowable, as they are based on claims 119-122 as originally filed.

Claims 39-50 are based on original claims 5, 15, 17, 26, 29, 32, 45, 68, 78, 87, 94, 106 and therefore allowable.

Claims 51-56 are based on original claims 125-130 and therefore allowable.

The compound according to claim 57 is a preferred embodiment that has no basis in the application as originally filed and is therefore not allowable under Articles 19(2) and 34(2)(b) PCT. The same objection must consequently be applied for the dependent claims 58 and 59.

The amended pages 4 and 27 of the description fulfil the requirements of Articles 19(2) and 34(2)(b) PCT.

The compounds GS-8361 and GS 17432 according to p. 2195 of D2 are representatives of the compounds I according to the present case.

The compound 9-[2-(Phosphonomethoxy)ethyl]2-amino-6-cyclopropylaminopurine cited in Table I of D1 is a representative of the compounds according to claim 28.

By consequence the subject-matter of claims 1-32, 37-38 and 51 is not novel in the sense of Article 33(2) PCT.

The compounds disclosed in D2 are known as displaying antiviral activities, however the use thereof against cancer or HPV is not mentioned.

Representatives of the compounds I according to the present case are prodrugs of the compound cyclopropylPMEDAP which is, according to D4, suitable against the papillomavirus.

D4 is considered the closest prior art.

The problem underlying the present case therefore has to be formulated as to provide further nucleotide analog amidates which are suitable for the treatment of the human papilloma virus.

Representatives of the compounds I are a solution to the problem, as has been shown in the description.

Concerning their activity against HPV the compounds I have to be considered an obvious solution to the problem, tt is, however, not indicated in D2 or D4 that the compounds disclosed therein are also suitable for the treatment of proliferative diseases such as cancer.

As the latter can be considered an unexpected effect those compounds I which are novel cannot be considered obvious for the skilled man.

Consequently an inventive step in the sense of Article 33(3) PCT is acknowledged for the subject-matter of claims 33-36, 39-50 and 57-59.

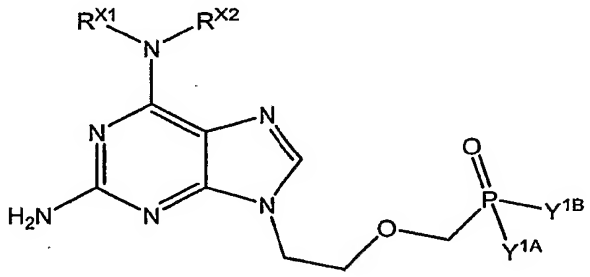
Further objections:

Claim 28 cannot be considered a dependent claim, as according to claim 1 at least one of Y1A or Y1B is a $N(R^x)$ (Art. 6 PCT).

As such there exists an unmet need for effective HPV treatment. It has now been surprisingly discovered compounds that meet this need, and provide other benefits as well. Relevant background art: Snoeck et al., Antimicrobial Agents and Chemotherapy, vol. 46(11), pp. 3356 – 3361 (Nov. 2002); Keith et al., Antimicrobial Agents and Chemotherapy, vol. 47(7), pp. 2193-2198 (July 2003); Christensen et al., Antiviral Research, vol. 48, pp. 131-142 (2000); U.S. Patent Publication No. 2003/0072814 A1; U.S. Patent 5,798,340; and PCT Application No. PCT/CZ96/00011.

SUMMARY OF THE INVENTION

A compound of formula I,



I

wherein:

Y^{1A} and Y^{1B} are independently Y^1;

R^{X1} and R^{X2} are independently R^X;

Y^1 is =O, -O(R^X), =S, -N(R^X), -N(O)(R^X), -N(OR^X), -N(O)(OR^X), or -N(N(R^X)(R^X));

R^X is independently R^1, R^2, R^4, W^3, or a protecting group;

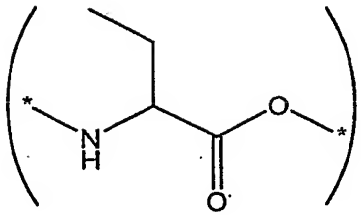
R^1 is independently -H or alkyl of 1 to 18 carbon atoms;

R^2 is independently R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

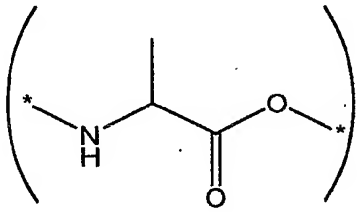
R^{3a} is -H, -F, -Cl, -Br, -I, $-CF_3$, -CN, N_3, $-NO_2$, or $-OR^4$;

R^{3b} is =O, -O(R^4), =S, -N(R^4), -N(O)(R^4), -N(OR^4), -N(O)(OR^4), or -N(N(R^4)(R^4));



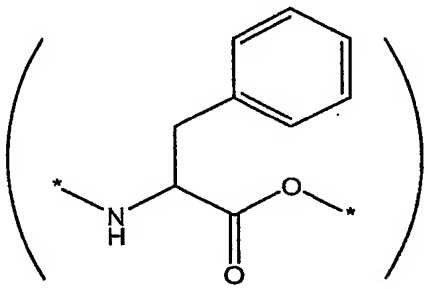
where the points of attachment are designated by the " * ".

As used herein the term "Ala" refers to a divalent moiety of alanine,



where the points of attachment are designated by the " * ".

As used herein the term "Phe" refers to a divalent moiety of phenyl alanine,

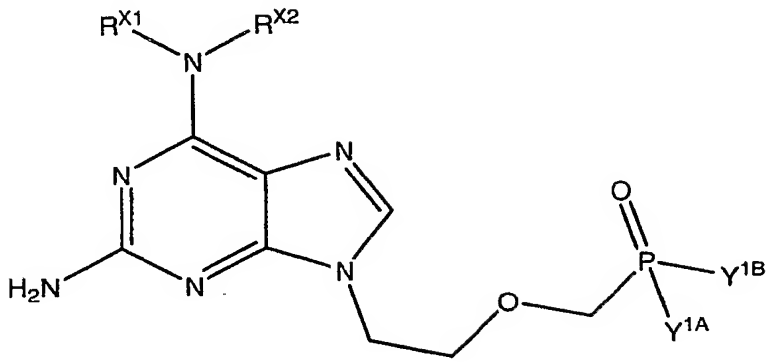


where the points of attachment are designated by the " * ".

As used herein the term "POC" refers to the divalent moiety of hydroxymethyl isopropyl carbonate,

What Is Claimed:

1. A compound of Formula I,



I

wherein:

Y^{1A} and Y^{1B} are independently Y^1;

R^{X1} is H and R^{X2} is W^5;

Y^1 is =O, -O(R^X), =S, -N(R^X), -N(O)(R^X), -N(OR^X), -N(O)(OR^X), or -N(N(R^X)(R^X)) provided that at least one Y^1 is –N(R^X);

R^X is independently R^1, R^2, R^4, W^3, or a protecting group;

R^1 is independently -H or alkyl of 1 to 18 carbon atoms;

R^2 is independently R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is -H, -F, -Cl, -Br, -I, -CF_3, -CN, N_3, -NO_2, or –OR^4;

R^{3b} is =O, -O(R^4), =S, -N(R^4), -N(O)(R^4), -N(OR^4), -N(O)(OR^4), or -N(N(R^4)(R^4));

R^{3c} is –R^4, -N(R^4)(R^4), -SR^4, -S(O)R^4, -S(O)$_2R^4$, -S(O)(OR^4), -S(O)$_2$(OR^4), -OC(R^{3b})R^4, -OC(R^{3b})OR^4, -OC(R^{3b})(N(R^4)(R^4)), -SC(R^{3b})R^4, -SC(R^{3b})OR^4, -

$SC(R^{3b})(N(R^4)(R^4))$, $-N(R^4)C(R^{3b})R^4$, $-N(R^4)C(R^{3b})OR^4$, $-N(R^4)C(R^{3b})(N(R^4)(R^4))$, W^3 or $-R^5W^3$;

R^{3d} is $-C(R^{3b})R^4$, $-C(R^{3b})OR^4$, $-C(R^{3b})W^3$, $-C(R^{3b})OW^3$ or $-C(R^{3b})(N(R^4)(R^4))$;

R^4 is -H, or an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2 to 18 carbon atoms;

W^3 is W^4 or W^5;

W^4 is R^6, $-C(R^{3b})R^6$, $-C(R^{3b})W^5$, $-SO_{M2}R^6$, or $-SO_{M2}W^5$, wherein R^6 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups; and

M2 is 0, 1 or 2;

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1 wherein Y^{1A} and Y^{1B} are $-N(R^X)$.

3. The compound of claim 2 wherein R^X is R^2.

4. The compound of claim 3 wherein R^2 is R^4 substituted with R^{3d}.

5. The compound of claim 4 wherein R^4 is ethyl substituted with R^{3d}.

6. The compound of claim 5 wherein R^{3d} is $-C(R^{3b})OR^4$.

7. The compound of claim 6 wherein R^{3b} is =O.

8. The compound of claim 7 wherein R^4 is alkyl of 1 to 18 carbon atoms.

9. The compound of claim 1 wherein R^{3d} is $-C(R^{3b})OW^3$.

10. The compound of claim 1 wherein R^4 is propyl substituted with R^{3d}.

11. The compound of claim 1 wherein R^{3d} is $-C(R^{3b})OR^4$.

12. The compound of claim 3 wherein R^2 is R^4 independently substituted with two R^3 groups.

13. The compound of claim 12 wherein R^4 is methyl substituted with two R^3 groups.

14. The compound of claim 13 wherein one R^3 group is R^{3c}.

15. The compound of claim 1 wherein R^5 is methylene.

16. The compound of claim 1 wherein W^3 is W^5.

17. The compound of claim 14 wherein one R^3 group is R^{3d}.

18. The compound of claim 1 wherein R^{3c} is W^3.

19. The compound of claim 1 wherein Y^{1A} is $-N(R^X)$ and W^5 is a carbocycle.

20. The compound of claim 1 wherein Y^{1B} is $-N(R^X)$.

21. The compound of claim 1 wherein R^{3c} is $-R^5W^3$.

22. The compound of claim 16 wherein W^5 is a carbocycle.

23. The compound of claim 1 wherein Y^{1B} is $-O(R^X)$.

24. The compound of claim 23 wherein Y^{1B} is $-O(W^3)$.

25. The compound of claim 22 wherein said carbocycle is phenyl.

26. The compound of claim 1 wherein R^2 is R^4 substituted with R^{3c} and R^{3d}.

27. The compound of claim 26 wherein R^4 is ethyl substituted with R^{3c} and R^{3d}.

28. The compound of claim 1 wherein Y^{1A} and Y^{1B} are $-O(R^X)$.

29. The compound of claim 1 wherein R^{X2} is R^4.

30. The compound of claim 1 wherein R^2 is R^4 substituted with one R^3.

31. The compound of claim 30 wherein R^4 is methyl substituted with one R^3.

32. The compound of claim 31 wherein R^3 is R^{3a}.

33. The compound of claim 32 wherein R^{3a} is $-CF_3$.

34. The compound of claim 30 wherein R^4 is $-CH_2$-CF_3.

35. The compound of claim 1 for use as an antiproliferative agent.

36. The compound of claim 1 for use as an apoptotic agent.

37. The compound of claim 1 for use as an anti-HPV agent.

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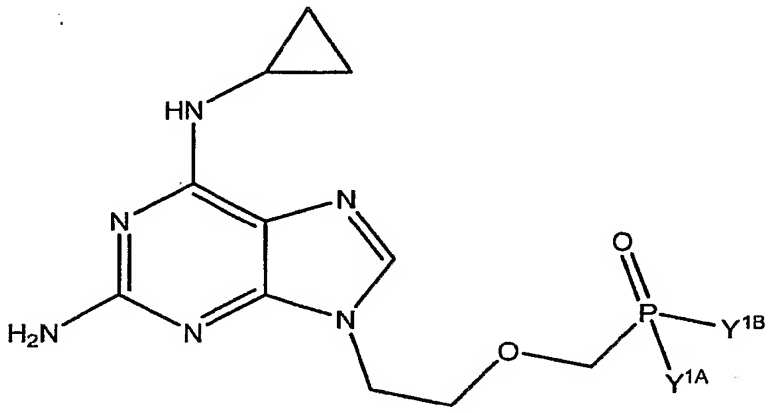
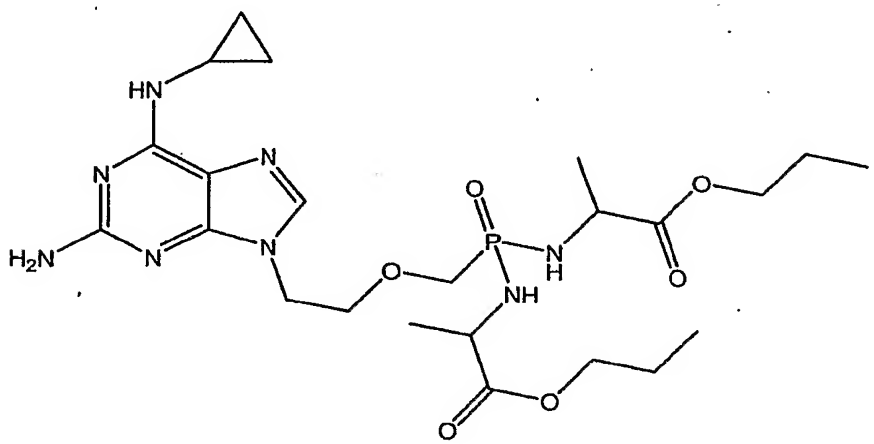
38. The compound of claim 1 for use as a topical anti-HPV agent.

39. The compound of claim 1 of the Formula IA,



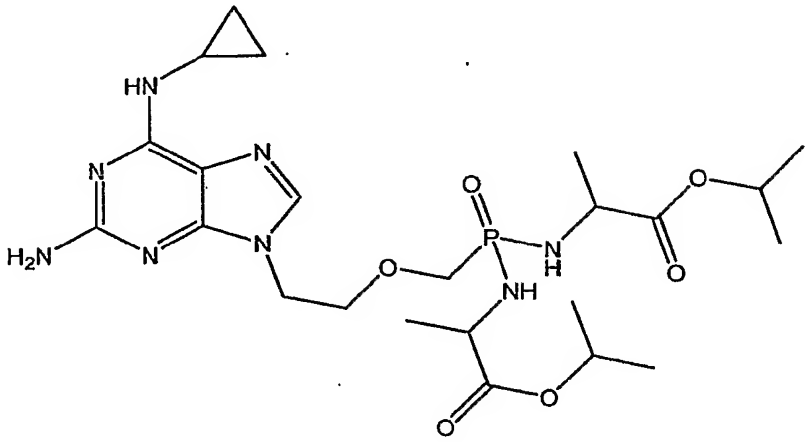
10 IA

40. The compound of claim 1 of the formula,

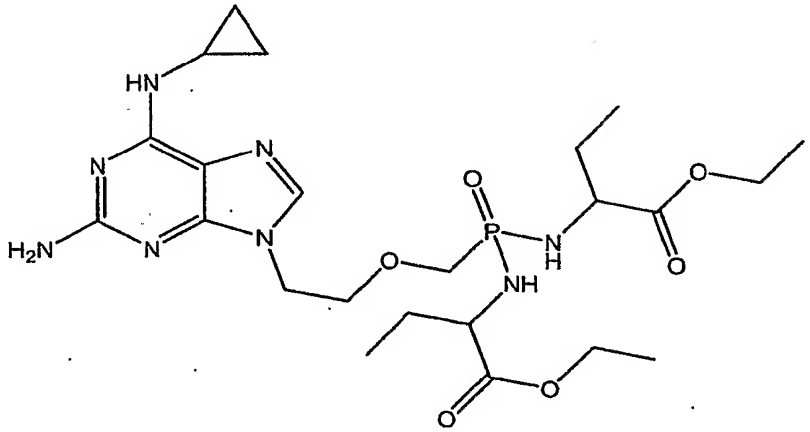


5 AMENDED SHEET 31/10/2005

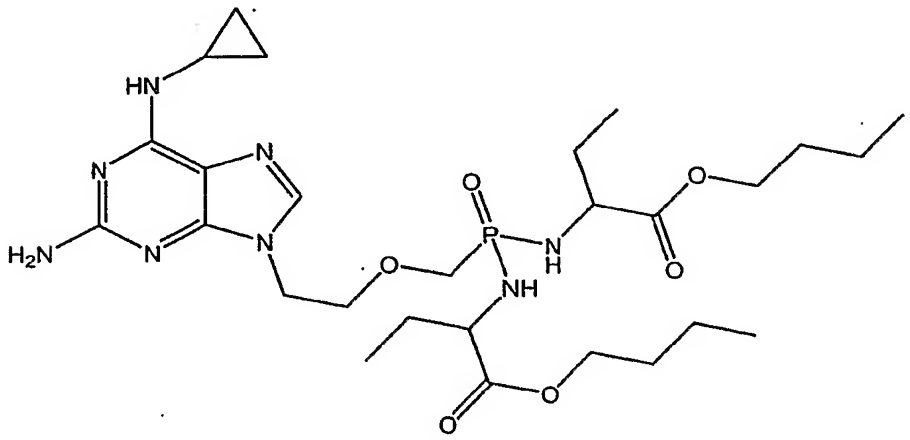
41. The compound of claim 1 of the formula,



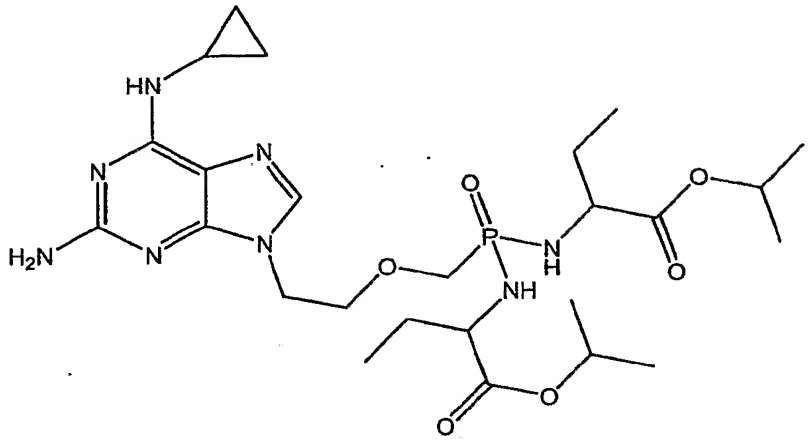
42. The compound of claim 1 of the formula,



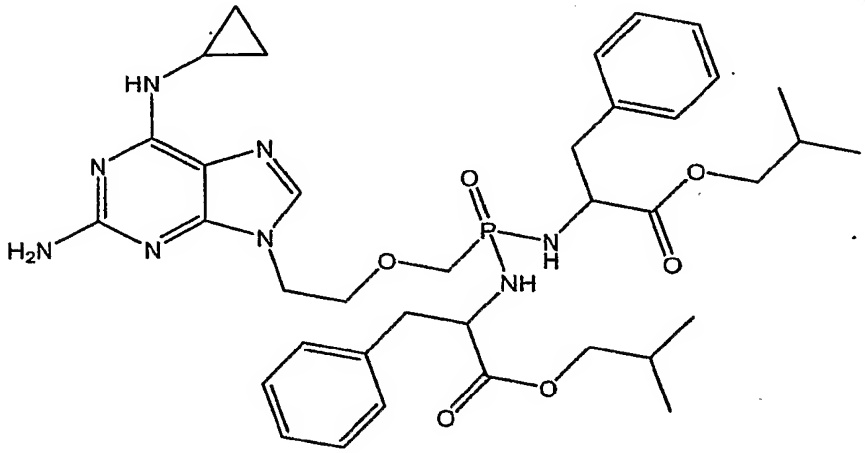
43. The compound of claim 1 of the formula,



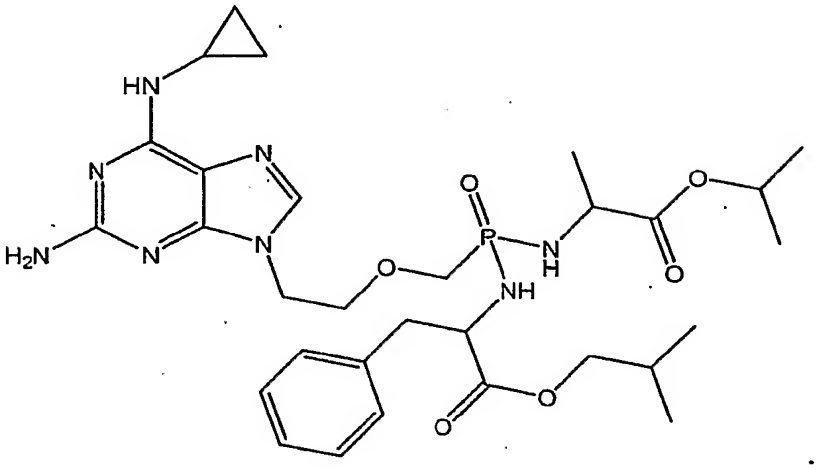
44. The compound of claim 1 of the formula,



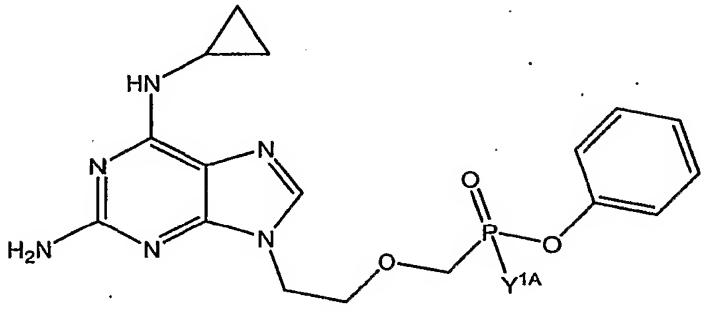
45. The compound of claim 1 of the formula,



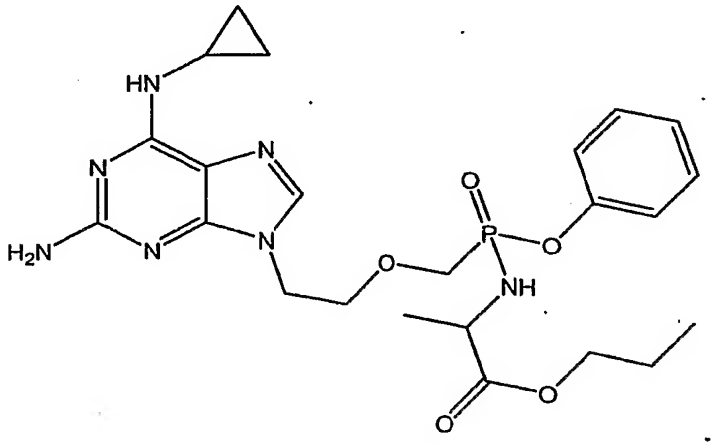
46. The compound of claim 1 of the formula,



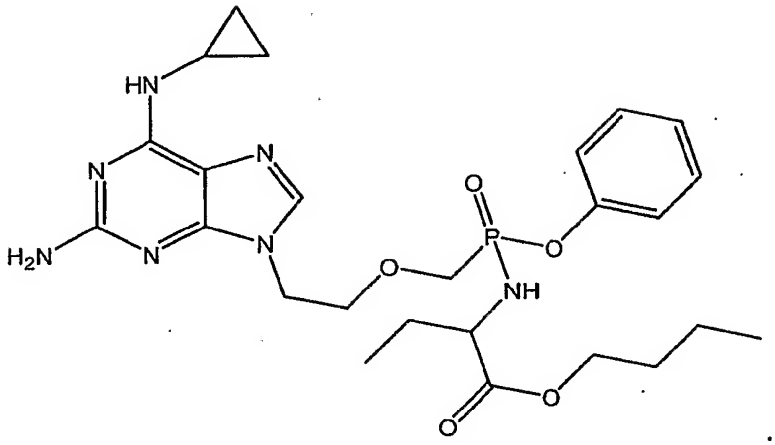
47. The compound of claim 1 of the formula,



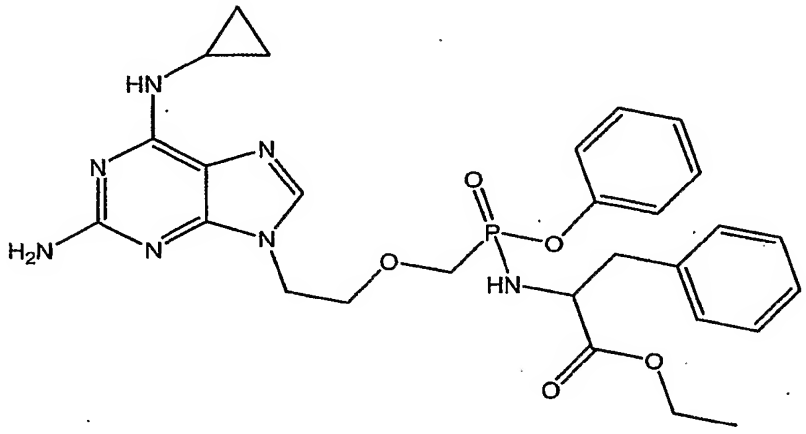
48. The compound of claim 1 of the formula,



49. The compound of claim 1 of the formula,



50. The compound of claim 1 of the formula,



51. A pharmaceutical composition comprising an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

52. The pharmaceutical composition of claim 51 where said composition is a gel composition.

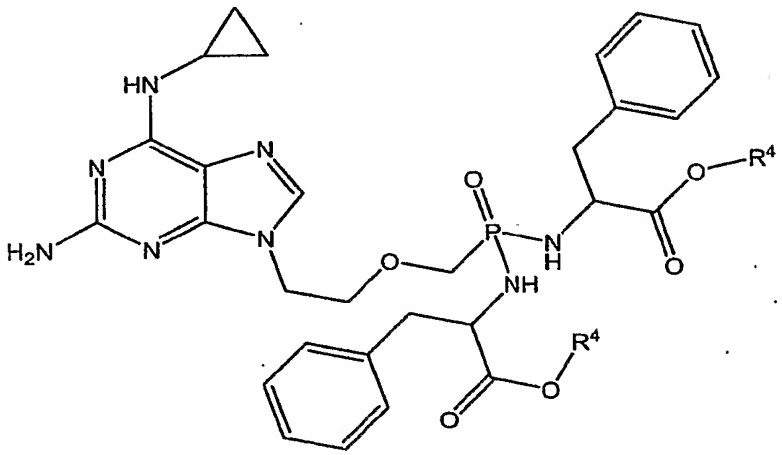
53. The pharmaceutical composition of claim 51, where said composition is an ointment composition.

54. A pharmaceutical composition comprising an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, and an effective amount of at least one antiviral agent, and a pharmaceutically acceptable carrier.

55. The pharmaceutical composition of claim 54, where said composition is a gel composition.

56. The pharmaceutical composition of claim 54, where said composition is an ointment composition.

57. A compound of the formula,



wherein R^4 is H, or an alkyl of 1 to 18 atoms, alkenyl of 2 to 18 carbon atoms or alkynyl of 2 to 18 carbon atoms and pharmaceutically acceptable salts thereof.

58. A gel or ointment comprising the compound of claim 57.

59. The ointment or gel of claim 58 for use as an antiproliferative, apoptotic or anti-HPV agent.